

Remarks**A. Status of the Claims**

Claims 20-22, 24, 26-29, 31 and 33 were pending for purposes of the Office Action and remain in the application, as amended herein, in accordance with the foregoing claim listing. Claims 1-19, 23, 25, 30, 32 and 34-38 were previously canceled without prejudice.

With regard to the claim amendments in this Reply, independent Claims 20 and 27 have been amended to recite the claimed alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analogs, salts, or derivatives of 25(OH)D as a Markush group in order to clarify the exact analogs, salts, or derivatives that are within the scope of the claims. Support for this amendment is provided in the specification at page 18, lines 25, et seq., as indicated in the previous Reply.

Applicant respectfully submits that no new matter is added by virtue of these amendments.

Withdrawal of previous rejections

Applicants gratefully acknowledge the Examiner's careful consideration of the previous amendments and remarks and the acquiescence in overcoming all the previous prior art rejections.

Certain written description and enablement rejections are maintained, however, as modified in view of the amended claims. In addition, a new rejection under 35 USC §112, second paragraph, is also asserted. These rejections are addressed below.

Maintained Rejections – 35 U.S.C. §112

Claims 20-22, 24, 26-29, 31 and 33 are rejected under 35 USC §112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Office Action indicates that a person of ordinary skill in the art would not be apprised of the scope of the invention because the amounts for the claimed analogs, salts or derivatives of 25(OH)D could not be readily quantitated.

Applicants have amended the claims such that the claimed analogs, salts or derivatives of 25(OH)D are recited as part of a Markush group. The Markush format is believed to provide definiteness to the claim since the amounts readily quantitated by the person of ordinary skill in the art (as acknowledged in the Office Action) for the 25(OH)D would be the same as the claimed analogs, salts or derivatives of 25(OH)D, or would be readily quantitated without undue experimentation. Reconsideration and withdrawal of the maintained indefiniteness rejection under 35 USC §112, second paragraph, is respectfully requested.

Claims 20-22, 24, 26-29, 31 and 33 also stand rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. It appears that the issue regarding the written description revolves around how far one may deviate from the claimed alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analogs, salts, or derivatives of 25(OH)D. Clearly, the subject application provides written description for 25(OH)D and the alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified forms of 25(OH)D. Specifically, the specification provides at page 18 lines 25, et seq.:

Useful analogs, derivatives, or salts of 25(OH)D include alkylated, glycosylated, arylated, halogenated, or hydroxylated 25(OH)D, orthoesters of 25(OH)D, or pharmaceutical salts of 25(OH)D. These analogs, derivatives, or salts can be synthesized or otherwise manufactured by chemical procedures which are well-known and readily available to those of ordinary skill in the art. The vitamin D analogs can be obtained according to the methods disclosed in U.S. Pat. Nos. 5,508,392, 5,457,217, 5,414,098, 5,384,313, 5,373,004, 5,371,249, 5,430,196, 5,260,290, 5,393,749, 5,395,830, 5,250,523, 5,247,104, 5,397,775, 5,194,431, 5,281,731, 5,254,538, 5,232,836, 5,185,150, 5,321,018, 5,086,191, 5,036,061, 5,030,772, 5,246,925, 4,973,584, 5,354,744, 4,927,815, 4,857,518, 4,851,401, 4,851,400, 4,847,012, 4,755,329, 4,940,700, 4,619,920, 4,594,192, 4,588,716, 4,564,474, 4,552,698, 4,588,528, 4,719,204, 4,719,205, 4,689,180, 4,505,906, 4,769,181, 4,502,991, 4,481,198, 4,448,726, 4,448,721, 4,428,946, 4,411,833, 4,410,515, 4,367,177, 4,336,193, 4,360,472, 4,360,471, 4,307,231, 4,307,025, 4,358,406, 4,305,880, 4,279,826, and 4,248,791.

Thus, the subject application provides an express written description of the claimed analogs, salts, or derivatives of 25(OH)D as well as, by reference to issued patents describing those analogs, salts, or derivatives, an enabling description of how to make and use those analogs, salts, or derivatives of 25(OH)D.

In addition, the subject application provides for the use in accordance with the claimed invention of the claimed analogs, salts, or derivatives of 25(OH)D in the context of

25(OH)D, and are clearly intended to be used as the 25(OH)D is used, with any variation or deviation being within the purview of the ordinarily skilled artisan and without undue experimentation.

Moreover, the scope of the claim is now further clarified by the inclusion of a Markush group to expressly recite that the invention encompasses 25(OH)D and the alkylated, glycosylated, arylated, halogenated, hydroxylated or orthoesterified analogs, salts, or derivatives of 25(OH)D; the claims do not include analogs, salts, or derivatives of those analogs, salts or derivatives that would require undue experimentation by a person of ordinary skill in the art. Withdrawal of this 35 USC §112, first paragraph, rejection is respectfully requested upon reconsideration.

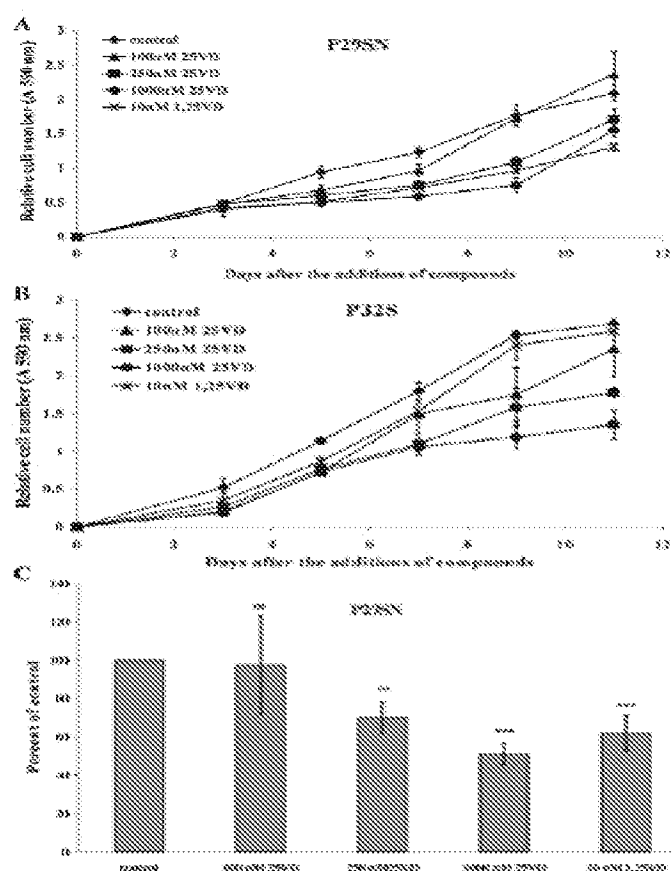
Claims 20-22, 24, 26-29, 31 and 33 also stand rejected under 35 USC §112, second paragraph, as failing to comply with the enablement requirement. However, as stated above, the claims now provide a Markush group to more clearly define the scope of the claims and, as also stated above, the compounds falling within the scope of the claims are believed to be enabled since a person of ordinary skill in the art is enabled use the compounds as specifically exemplified for 25(OH)D. Thus, no undue experimentation is required on the part of the ordinarily skilled artisan to practice the invention as described in the specification.

This rejection also appears to raise the issue of whether a person of ordinary skill in the art may *successfully* practice the invention. For example, the Office Action, at page 7 (mid-page), asserts that the specification is silent on the amount of 25(OH)D that may be converted to 1,25-dihydroxyvitamin D, the feasibility of such conversion, and the resultant inhibition of cancer or tumor cells by 25(OH)D or the claimed analogs, salts, or derivatives of 25(OH)D. The correlation between the claimed “effective amount” of 25(OH)D and the resulting successful inhibition of prostate cancer cells is established by the studies conducted, and published by, Lou, *et al.*, (copy attached) and is discussed in a Rule 132 Declaration by Dr. Gary G. Schwartz, submitted herewith.

In direct contrast to the speculative conclusions drawn by the cited Ma, *et al.*, Hsu, *et al.*, and Whitlach, *et al.*, references that 25(OH)D may not inhibit cancer or tumor cells, the Schwartz Rule 132 Declaration shows that Lou, *et al.*, a Finnish group independent of the inventor, establish the successful inhibition of prostate cancer cells by 100-250 nM of

25-(OH)D₃, an amount within the range of the “effective amount” claimed in the subject application. The last sentence in the Lou, *et al.*, Abstract summarizes that “[a]ltogether our results suggest that 25OHD₃ at a high but physiological concentration acts as an active hormone with respect to vitamin D₃ responsive gene regulation and suppression of cell proliferation.”

In addition, the successful results are illustrated in Figure 2 from the Lou, *et al.*, publication, reproduced below, which clearly shows significant inhibition of prostate cancer cell growth by 25(OH)D.



Effects of 25(OH)D₃ and 1α,25-(OH)₂D₃ on the growth of human primary prostatic stromal cells. P298N 15 (B) cells were treated with vehicle (0.1% ethanol), 100, 250, 1000 nM of 25(OH)D₃ (25VD₃) and 10 nM of 1,25VD₃ for 11 days, and relative cell numbers were determined at Days 3, 5, 7, 9, and 11 using a *wt* assay. The relative growth of P298N cells at Day 9 is shown in (C). Two separate experiments were in which six determinations were made. Statistical significance was evaluated by Student's *t*-test, **p* < 0.01, ****p* < 0.001, ns = not significant, *P* < 0.05.

Having established a correlation between the claimed “effective amount” of 25(OH)D and cancer cell inhibition, reconsideration and withdrawal of the enablement rejection under 35 USC §112, second paragraph, is requested upon reconsideration.

New Rejection – 35 USC §112, second paragraph

Claims 20-22, 24, 26-29, 31 and 33 have been newly rejected under 35 USC §112, second paragraph, as being incomplete for omitting essential elements. The Office Action specifies that essential elements are “a correlation between the effective amount and the preamble”, i.e., a method of inhibiting cancer or tumor cells. Applicants respectfully traverse in view of the clear showing of a correlation between the effective amount and the preamble as presented by Lou, *et al.*, as discussed above. Thus, because there is a clear and complete showing of a correlation between the effective amount and the preamble (inhibition of cancer or tumor cells), applicants believe there is no omission of essential elements, and that the claims and specification meet all requirements of 35 USC §112. Reconsideration and withdrawal of the rejection under 35 USC §112, second paragraph, is respectfully requested.

Conclusion

In accordance with the foregoing amendments to the claims and accompanying remarks, applicant believes the claims to meet all the requirements of 35 USC §112 and believe this case to be in condition for allowance. Such action is earnestly solicited without further delay.

Applicants further invite the Examiner to call the undersigned if clarification is needed on any aspect of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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